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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C07H 21/04, C12Q 1/68, C07K 5/00

A3

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09/085,199 27 May 1998 (27.05.98) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
20 April 2000 (20.04.00)

(54) Title: APOPTOSIS MODULATORS THAT INTERACT WITH THE HUNTINGTON'S DISEASE GENE

(57) Abstract

A family of proteins, including a specific human protein designated as HIP1, has been identified that interact differently with the gene product of a normal (16 CAG repeat) and an expanded (>44 CAG repeat) HD gene. Expression of the HIP1 protein was found to be enriched in the brain. Analysis of the sequence of the HIP1 protein indicated that it includes a death effector domain (DED), suggesting an apoptotic function. Thus, it appears that a normal function of Huntingtin may be to bind HIP1 and related apoptosis modulators, reducing its effectiveness in stimulating cell death. Since expanded huntingtin performs this function less well, there is an increase in HIP1–modulated cell death in individuals with an expanded repeat in the HD gene. This understanding of the likely role of huntingtin and HIP1 or related proteins (collectively "HIP–apoptosis modulating proteins") in the pathology of Huntington's disease offers several possibilities for therapy. First, because the function of huntingtin apparently depends at least in part on the ability to interact with HIP–apoptosis modulating proteins, added expression (e.g., via gene therapy) of normal (non–expanded) huntingtin or of the HIP–binding region of huntingtin should provide a therapeutic benefit. Other DED–interacting peptides could also be used to mask and reduce the interaction of HIP–apoptosis modulating proteins with the death signaling complex. Alternatively, a mutant form of HIP–protein from which the DED has been deleted might be introduced, for example using gene therapy techniques. Because HIP–apoptosis modulating proteins have been shown to self–associate, a protein with a deleted DED may compete with endogenous HIP–protein in the formation of these associations, thereby reducing the amount of apoptotically–active HIP–protein.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11743

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07H 21/04; C12Q 1/68; C07K 5/00
US CL :536/23.5; 435/6; 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5; 435/6; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPAT, CAPLUS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANKER et al., HIP-I: A Huntingtin Interacting Protein Isolated by the Yeast Two-hybrid System. Human Molecular Genetics. March 1997, Vol. 6, No. 3, pages 487-495, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 DECEMBER 1999	Date of mailing of the international search report 3 February 2000 (03.02.00)
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SCOTT HOUTTEMAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

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PCT/US99/11743

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 March 2000 (08.03.00)	
International application No. PCT/US99/11743	**Applicant's or agent's file reference** UBC.P-013WO2
International filing date (day/month/year) 27 May 1999 (27.05.99)	**Priority date** (day/month/year) 27 May 1998 (27.05.98)
Applicant KALCHMAN, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 December 1999 (13.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

3150930

PATENT COOPERATION TREATY

RECD 25 SEP 2000

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MC010-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/11743	International filing date *(day/month/year)* 27 MAY 1999	Priority date *(day/month/year)* 27 MAY 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): C07H 21/04; C12Q 1/68; C07K 5/00 and US Cl.: 536/23.5; 435/6; 530/350		
Applicant [MERCK FROSST ~~CANADA AND~~ CO.]* UNIVERSITY OF BRITISH COLUMBIA.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☑ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13 DECEMBER 1999	15 AUGUST 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SCOTT HOUTTEMAN Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/11743

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. 7-8, 10-11

☒ the drawings, sheets/~~fig~~ NONE

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/11743

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-6, 9, 12-15	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-6, 9, 12-15	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-6, 9, 12-15	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-6, 9, 12-15 meet the criteria set out in PCT Article 33(2)-(4). The closest prior art Wanker et al. teach an HD-interacting polypeptide expression vector. Wanker et al., however, does not teach or fairly suggest the claimed HD interacting protein encoded by SEQ ID NOS. 2, 4 5 or 7 nor the methods of use of HD interacting proteins in reducing apoptosis or in screening for apoptosis inhibiting activity.

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-31, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) NONE, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 32-33, filed with the letter of 15 August 2000.

This report has been drawn on the basis of the drawings,
page(s) 1-12, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) 1-44, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

CLAIMS

1. A polypeptide comprising the sequence given by Seq. ID. No. 5.

2. A cDNA molecule comprising the sequence given by Seq. ID No. 6.

3. A polypeptide comprising the sequence given by Seq. ID No. 7.

4. A method for ameliorating the effects of Huntington's disease in a patient expressing a HIP-apoptosis modulating protein, comprising the step of administering the patient a therapeutic composition which reduces the activity of the HIP-apoptosis modulating protein.

5. A method according to claim 4, wherein the composition comprises a material which binds to HIP-apoptosis modulating protein.

6. The method according to claim 4, wherein the composition comprises an expression vector encoding huntingtin having a normal number of repeats.

7. An expression vector for expression of a gene in a mammalian host comprising a region encoding an HD-interacting polypeptide.

8. The expression vector according to claim 7, wherein the HD-interacting polypeptide is an HIP-apoptosis modulating protein.

9. The expression vector according to claim 8, wherein the HIP-apoptosis modulating protein has a sequence which includes the amino acid sequences given by SEQ ID Nos. 2, 4, 5 or 7.

10. The expression vector of claim 7, wherein the HD-interacting polypeptide interacts differently with expanded Huntingtin than with Huntingtin having a CAG repeat region containing 15 to 35 repeats.

11. The expression vector according to claims of claims 7-10, further comprising a region encoding Huntingtin having a polyglutamine tract of 35 or fewer.

12. A method for inducing apoptotic death in cells, comprising the step of introducing into the cells an expression vector encoding at least the death effector domain of a HIP-apoptosis modulating protein whereby the death effector domain is expressed by the cells.

13. The method of claim 12, wherein the expression vector encodes the amino acid sequence given by Seq. ID. No. 2.

14. The method of claim 12, wherein the expression vector encodes the amino acid sequence given by Seq. ID. No. 4.

15. A method for screening a composition for the ability to inhibit apoptosis induced by an HIP-apoptosis modulating protein, comprising simultaneously exposing a population of cells to the composition and an HIP-apoptosis modulating protein and measuring the extent of cell death.

PATENT COOPERATION TREATY

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NOTE ON INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US99/11743	MC010-PCT	15 AUGUST 2000

Applicant
MERCK FROSST CANADA AND CO.,

Communication	Participants			
[X] by telephone	[ ] Applicant:	[X] identity checked	[ ] authorization checked	[ ] personally known
[ ] personal	[X] Agent: Mr. Joseph A. Coppola			
	[X] Examiner(s): SCOTT HOUTTEMAN			

Summary of communication:

The examiner and the applicant's rep. agreed to claim amendments.

[ ] ~~An extension of time limit is granted (Form PCT/IPEA/427).~~

[X] A copy of this note is being sent to the applicant with Form ~~PCT/IPEA/429.~~ PCT/IPEA/424.

Applicant/Agent	Authorized officer of IPEA/US
Mr. Joseph A. Coppola	SCOTT HOUTTEMAN
	Telephone No. (703) 308-0196

Form PCT/IPEA/428 (July 1992)★